CLAIMS

1. A hyaluronic acid derivative in which an anti-inflammatory drug is bound to hyaluronic acid through a covalent bond via a spacer having a biodegradable region.

2. The hyaluronic acid derivative according to claim 1, wherein the anti-inflammatory drug is selected from a non-steroidal anti-inflammatory drug and a disease-modifying anti-rheumatic drug.

3. The hyaluronic acid derivative according to claim 1 or 2, wherein the anti-inflammatory drug has a carboxyl group.

4. The hyaluronic acid derivative according to claim 3, wherein the anti-inflammatory drug is a residue of a compound selected from the group consisting of salicylic acid, aspirin, mefenamic acid, tolfenamic acid, flufenamic acid, diclofenac, sulindac, fenbufen, indometacin, acemetacin, amfenac, etodolac, felbinac, ibuprofen, flurbiprofen, ketoprofen, naproxen, pranoprofen, fenoprofen, tiaprofenic acid, oxaprozin, loxoprofen, alminoprofen, zaltoprofen, piroxicam, tenoxicam, lornoxicam, meloxicam, tiaramide, tolmetin, diflunisal, acetaminophen, floctafenine, tinoridine and actarit.

5. The hyaluronic acid derivative according to any one of claims 1 to 4, wherein the spacer is a compound having at least one functional group which binds to the hyaluronic acid and one functional group which binds to the anti-inflammatory drug.

6. The hyaluronic acid derivative according to any one of claims 1 to 5, wherein the spacer is selected from a diaminoalkane having from 2 to 18 carbon atoms, an aminoalkyl alcohol having from 2 to 12 carbon atoms which may have a substituent(s), and an amino acid.

7. The hyaluronic acid derivative according to any one of claims 1 to 6, wherein the hyaluronic acid has a weight average molecular weight of from 500,000 to 3,000,000.

8. The hyaluronic acid derivative according to any one of claims 1 to 7, wherein the anti-inflammatory drug is introduced at a ratio of from 5 to 50 mol% per repeating disaccharide unit of hyaluronic acid.

9. A hyaluronic acid derivative in which a non-steroidal anti-inflammatory drug is bound to hyaluronic acid through a covalent bond, which has a partial structure of hyaluronic acid disaccharide unit into which the anti-inflammatory drug is introduced is represented by the following formula (1):

$$Y\text{-}CO\text{-}NH\text{-}R^1\text{-}(O\text{-}R^2)_n \qquad (1)$$

wherein Y-CO- represents one residue of the hyaluronic acid disaccharide unit;

R^2 represents a non-steroidal anti-inflammatory drug residue represented by Z-CO- or hydrogen atom, with the proviso that all R^2's are not hydrogen atoms;

$-HN\text{-}R^1\text{-}(O\text{-})_n$ represents a spacer residue in a spacer compound represented by $H_2N\text{-}R^1\text{-}(OH)_n$ having n numbers of a hydroxyl group;

R^1 represents a linear or branched hydrocarbon group having from 2 to 12 carbon atoms which may have a substituent;

-CO-NH- represents an amide bond of a carboxyl group in glucuronic acid as a constituting saccharide of the hyaluronic acid with an amino group in the spacer compound;

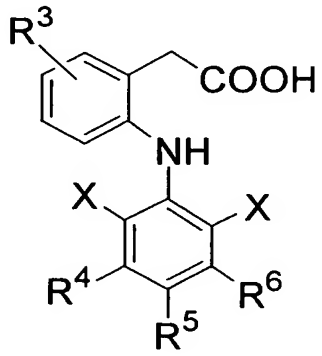
-O-CO- represents an ester bond of a hydroxyl group in the spacer compound with a carboxyl group in the non-steroidal anti-inflammatory drug residue; and

n is an integer of from 1 to 3,

wherein the hyaluronic acid derivative has a degree of substitution of the non-steroidal anti-inflammatory drug of from 5 to 50 mol% per repeating disaccharide unit of hyaluronic acid, and

the carbonyl group in a hyaluronic acid residue constituting the hyaluronic acid derivative is present as an amide bond participating in the binding with the spacer-binding anti-inflammatory drug residue or as a free carboxyl group not participating therein, according to the degree of substitution of the non-steroidal anti-inflammatory drug residue.

10. The hyaluronic acid derivative according to claim 9, wherein the non-steroidal anti-inflammatory drug is a compound represented by the following formula (2):



(2)

wherein R^3 represents a substituent selected from a lower alkyl group and a lower alkoxyl group, or a hydrogen atom;

R^4, R^5 and R^6 each independently represents a substituent selected from a group consisting of a lower alkyl group, a lower alkoxyl group and a hydroxyl group, a halogen atom, or a hydrogen atom; and

X's are the same or different and each represents a substituent selected from a lower alkyl group and a trifluoromethyl group, or a halogen atom, and at least one of X's is a halogen atom.

11. The hyaluronic acid derivative according to claim 10, wherein the non-steroidal anti-inflammatory drug is diclofenac or a derivative thereof.

12. The hyaluronic acid derivative according to any one of claims 9 to 11, wherein R^1 in formula (1) is an ethylene group, a trimethylene group or a propylene group, which may have a substituent(s).

13. The hyaluronic acid derivative according to any one of claims 1 to 12, which is obtainable by a method comprising reacting hyaluronic acid with a spacer-bound anti-inflammatory drug, or reacting a spacer-bound hyaluronic acid with an anti-inflammatory drug, and adjusting the reaction solution to alkaline conditions.

14. The hyaluronic acid derivative according to any one of claims 1 to 13, wherein a solution obtained by dissolving the hyaluronic acid derivative in an aqueous medium to a concentration of 1.0% by weight is capable of passing through a porous filter having a pore size of 0.45 μm and a diameter of 25 mm, at a ratio of 2 mL per minute or more at a temperature of 24°C under pressure of 5.0 kg/cm^2.

15. The hyaluronic acid derivative according to any one of claims 1 to 13, wherein a solution obtained by dissolving the hyaluronic acid derivative in an aqueous

medium to a concentration of 1.0% by weight is capable of passing through a porous filter having a pore size of 0.22 μm and a diameter of 25 mm, at a ratio of 2 mL per minute or more at a temperature of 24°C under pressure of 5.0 kg/cm^2.

16. A hyaluronic acid derivative solution which is capable of being pushed out from an injector and which comprises the hyaluronic acid derivative according to any one of claims 1 to 15 dissolved in an aqueous medium.

17. The hyaluronic acid derivative solution according to claim 16, wherein the aqueous medium is an aqueous medium selected from phosphate buffered saline, saline and water for injection.

18. The hyaluronic acid derivative solution according to claim 17, which is sterilized through a filter.

19. A pharmaceutical agent which comprises the hyaluronic acid derivative according to any one of claims 1 to 15 as an active ingredient.

20. The pharmaceutical agent according to claim 19, which is an arthritis treating agent, an anti-inflammatory medicament or an analgesic.

21. The pharmaceutical agent according to claim 19 or 20, which is useful for parenteral administration.

22. The pharmaceutical agent according to claim 21, which is an injection useful for topical administration.

23. The pharmaceutical agent according to claim 21 or 22, which is an injection useful for intra-articular administration.

24. A pharmaceutical agent which is capable of being pushed out from an injector and which comprises a solution in which the hyaluronic acid derivative according to any one of claims 1 to 15, as an active ingredient, is dissolved in an aqueous medium.

25. A kit for injection of a hyaluronic acid derivative, which comprises the hyaluronic acid derivative solution according to any one of claims 16 to 18, which is filled in an injector capable of pushing out the solution.

26. The kit according to claim 25, wherein the filled solution is the pharmaceutical agent according to any one of claims 19 to 24.

27. A medical injection kit which is sealed with a plunger for medicament extrusion in such a manner that it can be slid and which comprises a syringe filled with a solution in which the hyaluronic acid derivative according to any one of claims 1 to 15 is dissolved in pharmaceutically acceptable phosphate buffered saline, saline or water for injection.

28. A derivative in which a spacer having a biodegradable region is bound with an anti-inflammatory drug via a covalent bond.

29. The derivative according to claim 28, wherein the spacer having a biodegradable region is a residue of a diaminoalkane, an aminoalkyl alcohol or an amino acid.

30. The derivative according to claim 28 or 29, wherein the spacer having a biodegradable region is a residue of a compound capable of binding two or more anti-inflammatory drugs to one mole of the spacer.

31. The derivative according to any one of claims 28 to 30, wherein the anti-inflammatory drug is a residue of a compound selected from the group consisting of salicylic acid, aspirin, mefenamic acid, tolfenamic acid, flufenamic acid, diclofenac, sulindac, fenbufen, indometacin, acemetacin, amfenac, etodolac, felbinac, ibuprofen, flurbiprofen, ketoprofen, naproxen, pranoprofen, fenoprofen, tiaprofenic acid, oxaprozin, loxoprofen, alminoprofen, zaltoprofen, piroxicam, tenoxicam, lornoxicam, meloxicam, tiaramide, tolmetin, diflunisal, acetaminophen, floctafenine, tinoridine and actarit.

32. The derivative according to any one of claims 28 to 31, wherein the covalent bond is an ester bond or an amide bond.

33. The derivative according to claim 32, which is represented by the following formula (3):

$$H_2N\text{-}R^1\text{-}(O\text{-}R^2)_n \qquad (3)$$

wherein R^2 represents a hydrogen atom or a non-steroidal anti-inflammatory drug residue represented by Z-CO-, with the proviso that all R^2's are not hydrogen atoms;

$H_2N\text{-}R^1\text{-}(O\text{-})_n$ represents a spacer residue in a spacer compound represented by $H_2N\text{-}R^1\text{-}(OH)_n$ having n numbers of hydroxyl group;

R^1 represents a linear or branched hydrocarbon group having from 2 to 12 carbon atoms which may have substituents;

-O-CO- represents an ester bond consisting of a hydroxyl group in the spacer compound and a carboxyl group in the non-steroidal anti-inflammatory drug residue; and

n is an integer of from 1 to 3.

34. A process for producing a hyaluronic acid derivative which comprises hyaluronic acid bound to an anti-inflammatory drug through a covalent bond via a spacer having a biodegradable region, said process comprising:

reacting hyaluronic acid with a spacer-bound anti-inflammatory drug, or

reacting a spacer-bound hyaluronic acid with an anti-inflammatory drug.

35. The process for producing a hyaluronic acid derivative according to claim 34, which comprises treating a solution of a reaction product of hyaluronic acid with a spacer-bound anti-inflammatory drug or a solution of a reaction product of a spacer-bound hyaluronic acid with an anti-inflammatory drug under alkaline conditions.